Autoimmune Diseases

Trying to Shut Off the Body's Friendly Fire

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Published: June 5, 2005

ROXANNE PEREZ had never really been sick in her life until, at age 27, the roof began falling in. During a Fourth of July weekend at the beach in 2000, she was rushed to an emergency room suffering from convulsions. In the months after, she had blood transfusions and her spleen removed. Then, in 2001, she suffered a heart attack that left her heart permanently weakened.

Ms. Perez, who lives in San Antonio, had to give up her job, her home and car and move in with her parents. Now 32, she suffers from frequent fatigue, made worse when she goes out in the sun, and takes 25 different drugs. She said she could never have children.

"I was at the prime of my life and it's like a bomb fell on me," she said.

The attack was the physiological equivalent of friendly fire. Ms. Perez has lupus and hemolytic anemia. Both are autoimmune diseases, in which the person's immune system, meant to defend against germs, instead directs its fury against the person's own tissues.

There are at least 80 autoimmune diseases, ranging from familiar ones like rheumatoid arthritis, psoriasis, multiple sclerosis and Type 1 diabetes to more obscure ones like pemphigus vulgaris. They affect 5 to 8 percent of the American population, or up to 23.5 million people, say estimates from the National Institutes of Health. Patient advocacy groups often give much higher estimates, and there is evidence that the incidence of some of the diseases is increasing.

Most of the victims are women - many, like Ms. Perez, in their childbearing years. There are at least eight women for every man who has lupus, scleroderma, thyroiditis and Sjogren's syndrome. Women also outnumber men, though not by as large a margin, for multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease.

The reasons for the gender disparity are not known, though there are theories. In fact, little is definitively known about the causes of autoimmune diseases or how to treat them. It has been more than 30 years since a new drug was approved for lupus, for instance, and the existing drugs have severe side effects.

But scientists are now using genetics and biotechnology to gradually unravel the mind-boggling complexity of the immune system.

"It's a very vibrant field right now," said Dr. Noel R. Rose, the director of the Center for Autoimmune Disease Research at Johns Hopkins University and chairman of a committee to coordinate the $600 million in autoimmune disease research at the N.I.H.

Even the formation of Dr. Rose's committee, required by an act of Congress in 2000, is a sign of progress. In the past, each disease was thought of separately, discouraging scientists from sharing findings that might apply to more than one disease. And since most of the diseases by themselves are rare, there was not much incentive for drug companies to develop treatments. That is changing.

"Just in the last five years, they are now considered a category like cancer is considered a disease category," said Virginia T. Ladd, president of the American Autoimmune Related Diseases Association, a patient advocacy group in Eastpointe, Mich. "Eventually we should have an autoimmunologist like we have an oncologist."

In autoimmune disease, something goes awry with the process in which the immune system learns to distinguish self from non-self, the body's own tissues from that of an invading germ.

The diseases can run in families and some people get more than one. "If you live long enough you get to collect them," said Ms. Ladd, who has lupus, antiphospholipid syndrome, pernicious anemia and vasculitis.

Scientists think that a combination of genes raises susceptibility. But evidence suggests that it takes an external factor to set off the disease. This could be something in the diet or a drug. But most attention is focused on infections by viruses or bacteria.

Rheumatic fever, for example, is a heart ailment incited by the bacterium that causes strep throat. In a small percentage of people, the immune system attacks a protein in the heart that closely resembles part of the bacterium.

As for the gender discrepancy, many scientists theorize that it results from women's hormones, like estrogen. This is partly because many of the ailments begin after puberty and tend to ease after menopause.

Another theory is that immune attacks are set off by the presence of cells from another person in the bloodstream; women retain some cells from fetuses after pregnancy.

Dr. John Harley of the University of Oklahoma Health Sciences Center and the Oklahoma Medical Research Foundation said he believed that women having two X chromosomes and men only one plays a role. Men who have an extra X chromosome, a rare condition called Klinefelter's syndrome, have a higher rate of lupus than other men, Dr. Harley reported at a conference.

Diagnosing autoimmune diseases can be difficult. Some women say it takes years of shuttling from doctor to doctor, often hearing that it is all in their heads.

"Every doctor has a specialty, and they only look through that one window," said Kerry Landhauser of West Islip, N.Y., who said it took six years for her Sjogren's syndrome to be diagnosed after she began experiencing bad headaches in 1997.

In Sjogren's, the immune system attacks moisture-producing glands like those that make saliva. At first, Mrs. Landhauser said, her dry mouth, a telltale symptom, was mistaken as a side effect of pills she was taking for her headaches.

Many autoimmune diseases are treated by suppressing the immune system with steroids or chemotherapy. But immune suppression leaves a person vulnerable to infections. It's "rather like taking a sledgehammer to the computer to try to slow it down," Dr. Harley said.

Newer treatments, many being developed by biotechnology companies, try to interfere with one part of the immune system rather than suppress it over all.

The biggest successes have been drugs that block tumor necrosis factor, a protein in the body that spurs inflammation. The three drugs in this class, Enbrel, Remicade and Humira, have had a major impact in slowing the joint damage caused by rheumatoid arthritis, and one or more of the drugs is also approved to treat psoriasis, Crohn's disease and ankylosing spondylitis.

But while the new biotech drugs seem to be better than steroids - and more expensive, costing more than $10,000 a year - they still dampen the immune system enough to raise the risk of infections or certain cancers.

That danger was illustrated in the case of Tysabri, a biotech drug that was heralded as a breakthrough for multiple sclerosis, then taken off the market in February after it was linked to a rare and often fatal viral brain infection.

An ideal treatment would stop only the immune-system attack responsible for the disease while leaving the rest of the system working normally. In the future, it may also be possible to replace damaged tissue using stem cells.

Scientists are also seeking ways to detect the diseases before symptoms appear, by finding telltale antibodies in the blood or through genetic markers. "We'd like to try to intervene before the train wreck," said Dr. Rose of Johns Hopkins and the N.I.H.

Perhaps no disease presents as great a challenge as lupus, which is often described as the prototypical autoimmune disorder because it is clearly marked by antibodies that attack some crucial components of the body.

A report by Dr. Rose's committee at the N.I.H., based on scientific papers, estimates that 240,000 people in the United States have systemic lupus erythematosus, the most common form of the disease. The Lupus Foundation of America, using data from phone surveys, estimates 1.5 million have some form of lupus.

Lupus is more common in African-Americans and Hispanics than in Caucasians. Some scientists suspect that the disease is incited by infection with Epstein-Barr virus, which causes mononucleosis.

A few decades ago, lupus killed as many as half its victims in a few years. While the use of steroids and other harsh drugs has cut that rate markedly, some deaths still occur.

While most autoimmune diseases involve an attack on a specific target - joints in rheumatoid arthritis or insulin-producing cells in diabetes - lupus can bring on attacks on many fronts, including the heart, joints and kidneys. It is also highly variable.

"I can be sitting in a support group of 15 women," said Stephanie Lanier, 29, of Plano, Tex. "No one has the same symptoms and medications."
The variability can make it hard to measure whether an experimental drug is working in a clinical trial, especially when patients are taking many other drugs.

La Jolla Pharmaceutical, a biotechnology company in San Diego, has spent more than a quarter of a billion dollars testing a drug to reduce the kidney damage that is a major cause of sickness and death from lupus.

The company said that the drug, Riquent, reduces the levels of certain antibodies found in the blood of lupus patients, which scientific evidence indicates is a good thing. But the Food and Drug Administration has declined to approve Riquent, saying the data do not prove that the drug actually reduces kidney damage.

The F.D.A. has issued proposed guidelines on how lupus drugs should be tested. And other companies are now testing potential treatments.

Most closely watched, perhaps, is Human Genome Sciences, which is testing a drug that blocks the action of a protein in the body called B lymphocyte stimulator, or BLyS (pronounced bliss). BLyS stimulates B cells, the type of blood cells that makes antibodies. So blocking BLyS could dampen the immune-system attacks.

Evidence for this comes from the observation that people with lupus tend to have abnormally high levels of BLyS in their blood, and animals with high levels of BLyS get a lupuslike disease, said Dr. David C. Stump, executive vice president at the company, which is in Rockville, Md.

ZymoGenetics, based in Seattle, and Serono, in Switzerland, are in early-stage human testing of a different drug to mop up BLyS in the bloodstream. Other approaches exist, too. Aspreva Pharmaceuticals, in Victoria, British Columbia, is testing the drug CellCept, now used to stop rejection of transplanted organs, as a lupus treatment. Genentech and Biogen Idec are testing Rituxan, which kills B cells and is used to treat non-Hodgkin's lymphoma.

"There are probably going to be 10 to 15 trials launched in the next two years in lupus," said Dr. Jill P. Buyon, a lupus expert at the New York University Medical Center "I think it is finally receiving the attention it needs to receive."